II. REMARKS

Preliminary Remarks

1-2, 4-9, 14, 24-29, 34-36, 41, 45-48 and 50-60 are canceled and new claims 61-92 are added.

New claims 61-92 correspond to the original claims, insofar as they were directed to tetravalent antibody heterodimers, and to methods for making tetravalent antibody heterodimers. In particular, all of the new claims are directed to a tetravalent antibody heterodimer comprising an anti-CD20 antibody and an anti-CD23 antibody, and to a method for producing such an antibody heterodimer wherein each antibody molecule retains its binding specificity following dimerization, as described in the specification; *e.g.*, in Example 4. New claims 62, 65, 74, 76, 80, and 84-92 are directed to the claimed invention wherein both antibodies of the heterodimer are IgG antibodies; *e.g.*, as described on page 12, line 7, and in original claim 4. New claims 63, 66, 75, 77, 81, and 85 are directed to the invention wherein both antibodies are IgG-1 antibodies; *e.g.*, as described on pages 8 (lines 3-43) and 22 (lines 5-7). New claims 65, 66, and 84-92 are directed to the invention wherein the anti-CD20 antibody is a chimeric antibody consisting of light and heavy chains of a human IgG antibody in which the variable regions are replaced with the light and heavy chain variable regions of murine C2B8 antibody; and the anti-CD23 antibody is a chimeric antibody consisting of light and heavy chains of a human IgG antibody in which the variable regions are replaced with the light and heavy chain variable regions of monkey 5E8 antibody. Such chimeric antibodies are described in the specification; *e.g.*, in the paragraph bridging pages 6-7 (C2B8) and on page 8, lines 2-4 (primatized 5E8). Skilled persons would have been able to obtain DNA nucleotide sequences encoding the antibody polypeptides of the claimed invention without undue effort. For example, the nucleotide sequences of the light and heavy chains of the C2B8 antibody are described in U.S. Patent No. 5,736,137, and the nucleotide sequences light and heavy chain variable regions of the 5E8 antibody are described in U.S. Patent No. 6,011,138. New claims 67-72 are directed to the details of the disclosed method for making a tetravalent antibody heterodimer, and relate to the subject matter of original claims 1 (part vi), 24-27, and 45. Such methods are described in pages 15-16, and in Example 3.

Patentability Remarks

35 U.S.C. §112, First Paragraph - Enablement

Claim 36 was rejected under 35 U.S.C. 112, first paragraph, because the specification allegedly does not enable one skilled in the art to make or use a tetravalent heterodimeric antibody comprising the chimeric p5E8 antibody. The office action observed that U.S. Patent No. 6,011,138 discloses the amino acid sequences of the light and heavy chain variable regions of the p5E8 antibody, but does not disclose the amino acid sequences of the antibody constant regions.

Claim 36 has been canceled. New claims 65, 66, 76, 77, and 84-92 refer to a "chimeric antibody consisting of light and heavy chains of a human IgG antibody in which the variable regions are replaced with the light and heavy chain variable regions of monkey 5E8 antibody." The specification describes the p5E8 antibody as a primatized antibody (see p. 4, lines 14-16, and p. 8, lines 2-4), which a skilled person would know is an antibody comprising constant regions of a human antibody and the light and heavy chain variable regions of an antibody of an Old World monkey. At the time the priority application was filed, methods for making recombinant DNA vectors encoding chimeric antibodies comprising human constant regions and the variable regions of an antibody from a non-human animal were well known. For example, such methods are described in U.S. Patent No. 5,736,137, which describes construction of recombinant vectors encoding the chimeric C2B8 antibody, and the use of such vectors to produce the chimeric antibodies in transfected cells. Given the amino acid sequences of the light and heavy chain variable regions of the p5E8 antibody, as well as the corresponding DNA nucleotide sequences, as set forth in U.S. Patent No. 6,011,138, a person skilled in the art would readily be able to make a chimeric antibody comprising human constant regions and the light and heavy chain variable regions of the p5E8 antibody. Accordingly, deposit of cells containing DNA sequences encoding the claimed antibodies is not required to enable one of skill in the art to make and use the claimed invention. Withdrawal of the rejection under 35 U.S.C. 112, first paragraph, is respectfully requested.

35 U.S.C. §103(a)

Claims 1-2, 4-9, 14, 24-29, 34-36, 41, and 45-48 were rejected under 35 U.S.C. 103(a) as being obvious in view Caron et al. (1992), Fanger et al. (1992), Cumber et al. (1992), U.S. Patent No. 6,011,138 (Reff et al.), Reff et al. (1994), and the 1994-95 Pierce Catalog (pages T-157, T-163-169). The newly submitted, pending claims are directed to a tetravalent antibody heterodimer comprising an anti-CD20 antibody and an anti-CD23 antibody, and to a method for producing such an antibody heterodimer wherein each antibody molecule retains its binding specificity following dimerization. The basis for rejecting the claimed anti-CD20/anti-CD23 heterodimeric antibody as being obvious under 35 U.S.C. 103(a) was most recently stated in the office action dated 8/28/02 (see pp. 10-13).

The applicants adamantly traverse the rejection of the pending claims as being obvious under 35 U.S.C. 103(a) in view of the cited references. The office actions of record fail to establish *prima facie* that it would have been obvious to one of ordinary skill in the art to practice the claimed method and make the claimed heterodimer comprising an anti-CD20 antibody and an anti-CD23 antibody in view of the prior art. In particular, the office actions fail to establish that the teachings of the cited references would have motivated one of ordinary skill in the art to select CD20 and CD23 from all of the known lymphocyte surface antigens as the two antigens to be targeted by a heterodimeric antibody comprising anti-CD20 and anti-CD23 antibodies according to the claimed invention.

U.S. Patent No. 6,011,138 of Reff et al. shows that the primatized anti-CD23 antibody p5E8 (col. 7) binds to the low affinity receptor for IgE (FceRII/CD23) and can be used to inhibit IgE production. The Reff et al. (1994) reference shows that the chimeric anti-CD20 antibody, C2B8, has B cell-depleting activity. The office action dated 8/28/02 describes the disparate activities of the anti-CD23 and anti-CD20 antibodies, and alleges that it would have been obvious to one of ordinary skill in the art to make the claimed heterodimer in order to obtain an heterodimeric antibody having both activities. The text of the rejection (from pages 12-13 of the office action dated 8/28/02) is reprinted below:

> "In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a method for producing a heterodimeric antibody molecule comprising two different

> antibodies which bind two antigens because Reff et al. [a] teach CD23, which is a member of the C-type lectin family, has been shown to interact with several other ligands...present on a variety of cell types (see column 2, lines 60-63) and the subject antiCD23 antibody (sic) are effective in treating any disease wherein inhibition of IgE production is therapeutically desirable" (column 38, lines 42-46) and Reff et al. [b] teach CD20 is on the surface of B-cell lymphomas and C2B8 showed the ability to bind to human C1q, mediate (sic) complement-dependent cell lysis of human B lymphoid cells. ... In addition, one skilled in the art would want to produce a heterodimeric anti-CD20 and anti-CD23 antibody because one skilled in the art would know that targeting the CD23 would result in lower levels of IgE and targeting the CD20 with C2B8 would result in the lysis of the B-cell."

The office action found descriptions of the physiological activities of the two antibodies of the claimed heterodimer in prior art references, and concluded that it would have been obvious to make the claimed invention in order to have an antibody that possesses both activities. The references cited by the office action provide no suggestion or motivation to one of ordinary skill in the art to combine an anti-CD20 antibody and an anti-CD23 antibody to produce a heterodimeric antibody that depletes B cells and also inhibits IgE production. Nor would the scientific and medical knowledge of one of ordinary skill in the art provide the requisite motivation. The applicants submit that the rejection is based on hindsight obtained purely from the description of the claimed invention in the present application.

At the time the invention was made, heterodimeric anti-CD20/anti-CD23 antibodies had not been described, and the physiological activities of such anti-CD20/anti-CD23 heterodimers were unknown. The prior art provided no suggestion that it might be desirable or beneficial to make and use an anti-CD20/anti-CD23 heterodimer in order to deplete a patient's B cells and inhibit IgE production at the same time. Rather than use the claimed invention, it is more likely that a person of ordinary skill in the art at the time the invention was made would have chosen to use monomeric or homodimeric anti-CD23 antibodies to inhibit IgE production by IgE-specific B cells without simultaneously disrupting normal B

cell-dependent immune functions by co-administration of anti-CD20 antibodies. Furthermore, a person of ordinary skill in the art would have recognized that B cell depletion compromises a patient's immune system and puts the patient at serious risk of infection. A skilled person would also have recognized that antibody therapy carries risks of serious side effects. A skilled person who wished to deplete a patient's B cells would therefore have been unlikely to subject a patient undergoing B cell depletion to even greater danger by administering a heterodimer comprising a B cell-depleting antibody and an IgE-inhibiting antibody without knowing the physiological activities of such a heterodimer. For example, a skilled person would not have been able to predict whether sufficient numbers of IgE-producing B cells would survive the B cell-depleting treatment to justify co-administering an IgE-inhibiting antibody, with its attendant risks of adverse side effects.

It appears that the suggestion to combine the references to obtain the claimed invention is found only in the disclosure of the invention in the present application. This is the essence of hindsight. "When a rejection depends on a combination of prior art references, there must be some teaching, suggestion, or motivation to combine the references." In re Rouffet, 149 F.3d 1350, 1355, 47 USPQ2d 1453, 1456 (Fed.Cir.1998) (citing In re Geiger, 815 F.2d 686, 688, 2 USPQ2d 1276, 1278 (Fed.Cir.1987)). Decisions by the Board of Appeals of the U.S. Patent and Trademark Office and by the Federal Courts have made it clear that the best defense against hindsight-based obviousness analysis is the rigorous application of the requirement for a showing of a teaching or motivation to combine the prior art references. See Ecolochem, Inc. v. Southern California Edison Co., 227 F.3d 1361; 56 U.S.P.Q.2d 1065 (C.A.Fed. - Cal., 2000), citing Dembiczak, 175 F.3d at 999, 50 USPQ2d at 1617. "Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability--the essence of hindsight." Id. When determining the patentability of a claimed invention which combines two known elements, 'the question is whether there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination.' " In re Beattie, 974 F.2d 1309, 1311-12, 24 USPQ2d 1040, 1042 (Fed.Cir.1992) (quoting Lindemann, 730 F.2d at 1462, 221 USPQ at 488)."

Not only is there no suggestion in the cited prior art references to practice the claimed method and make the claimed heterodimer; the combination of an anti-CD20 and an anti-

CD23 antibody in the claimed tetravalent heterodimer shows unexpected synergism in inducing apoptosis of $CD20^+$ B cell lymphoma cells, relative to the individual component antibodies. As described in Examples 8 and 10 and Figures 16 and 17, C2B8/p5E8 heterodimers induce apoptosis and inhibit growth of $CD20^+$ $CD23^+$ B cell lymphoma cells in a dose-dependent manner, whereas the same concentrations of the individual anti-CD20 or anti-CD23 antibodies have negligible apoptotic effect. This surprising and unexpected activity was neither described nor suggested in the prior art.

In view of the foregoing, the Applicants submit that at the time the invention was made, the claimed invention was not obvious to one of ordinary skill in the art in view of the cited references. It is therefore, respectfully requested that the rejection of the claims under 35 U.S.C. 103(a) in view of the prior art be withdrawn.

Conclusion

All rejections having been addressed, it is respectfully submitted that the present application is in condition for allowance and a Notice to that effect is earnestly solicited. If any points remain in issue, which the examiner feels may be best resolved through a personal or telephone interview, he is kindly requested to contact the undersigned attorney at the telephone number listed below.

Respectfully submitted,

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